PATENT SPECIFICATION

NO DRAWINGS

1,122,786

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Date of Application and filing Complete Specification: 27 Aug., 1965.

No. 36983/65.

Application made in Japan (No. 51992) on 12 Sept., 1964.

Application made in Japan (No. 63189) on 10 Nov., 1964.

Application made in Japan (No. 6772) on 9 Feb., 1965.

Two Applications made in Japan (Nos. 7232 and 7233) on 11 Feb., 1965.

Application made in Japan (No. 17093) on 24 March, 1965.

Complete Specification Published: 7 Aug., 1968.

Index at acceptance:—C2 V2

Int. Cl.:—C 07 d 99/12

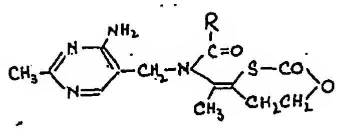
COMPLETE SPECIFICATION

Thiamine Derivatives

We, YAMANOUCHI SEIYAKU K.K., a Japanese Company of 5—1, Nihonbashi Honcho, 2-chome, Chuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel thiol-type thiamine derivatives more particularly to thiol-type thiamine derivatives having cyclic thiol carbonate structures wherein the S-position of the thiol group and the O-position of the β-hydroxyethyl group are bonded to the carbonyl group (—CO—) and the acid salts thereof, and further to a process for the production thereof. Furthermore, the invention relates to compositions containing the above compounds having pharmacological usefulness.

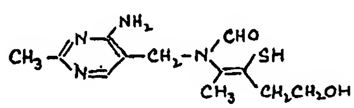
The above-mentioned thiol-type thiamine derivative of this invention is shown by the general formula



(I)

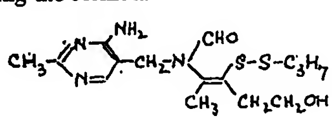
wherein R represents a hydrogen atom or an α-hydroxethyl group and when R represents the α-hydroxyethyl group, formula (I) means the optically active d-form, l-form, and nonactive dl-form. In the case, when R is a hydrogen atom, the compound shown by the above formula (I) can be called "carbothiamine" and if R is an α-hydroxyethyl group, the compound can be called "carbohydroxyethylthiamine".

Since the following thiol-type thiamine was reported by Zima et al (Zima et al.: Ber., *73*, 941 (1940))



various thiol-type thiamine derivatives have been synthesized.

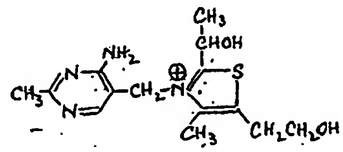
Among them, there are, as an active Vitamin B_1 compound having a rapid and prolonged Vitamin B_1 activity, commercially available S-acylthiamine derivatives, such as, S.O-diacetylthiamine, S.O-dibenzoylthiamine (cf. U.S. Patent No. 2,752,348), and S-benzoylthiamine-O-monophosphate (cf. U.S. Patent No. 3,064,000) and thiamine disulfide derivatives, such as, thiamine propyl disulfide (TPD) (cf. U.S. Patent No. 2,833,768) having the formula



thiamine-8-(methyl-6-acetyldihydrothioctate)-disulfide (TATD) (cf., U.S. Patent No. 3,098,856), and O-benzoyl thiamine disulfide (BTDS) (cf. U.S. Patent No. 3,109,000).

It is proposed that by the reaction of thiol-type thiamines and, for example, ethyl chlorocarbonate, S-carbalkoxy derivatives (cf. U.S. Patent No. 3,158,613) and O.S-dicarbalkoxy derivative (cf. Brit. Patent No. 944,641) can be obtained and that for obtaining these carbonyloxy derivatives, phosgene in alcohol can be used instead of an alkyl/halo carbonate (cf. Japanese Patent Publication No. 20,166/1964).

On the other hand, hydroxyethylthiamine (HET) shown by the following formula



having an α-hydroxyethyl group at the 2-position of the thiazolium ring was synthesized for the first time early in 1958 by Krampitz et al. J.Am.Chem. Soc. *80*, 5893—94 (1958)) and from the consideration that the compound is an effective intermediate for administrated thiamines, various studies have been made (Goedde: Intern. Z. Vitaminforsch, *33*, 18—40 (1963)).

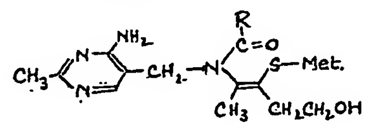
According to the configuration of α-hydroxyethyl group, optically active HET and nonactive HET are present.

An object of the present invention is to provide thiol-type thiamine derivatives of Formula (I) having unexpectedly excellent Vitamin B_1 activity as compared with thiamine and its known derivatives.

Another object of this invention is to provide novel thiol-type thiamine derivatives showing rapid and prolonged Vitamin B_1 activity. A further object of this invention is to provide active Vitamin B_1 agents suitable for oral administration.

A further object of the invention is to provide compositions of matter containing thiol-type thiamine derivatives which can be rapidly absorbed from the intestinal canal and when orally administered, a much more high (twice as high as TPD) level of Vitamin B_1 in blood than by thiamine propyl disulfide (TPD) known as typical active Vitamin B_1 agent is maintained for a long time.

Carbothiamine and carbohydroxyethylthiamine shown by Formula (I) may be prepared in a variety of different ways of which the more important can be expressed generically as comprising the interaction of basic salts of thiol-type thiamine or thiol-type hydroxyethyl thiamine (HET) represented by the formula II:



(II)

wherein R has the same significance as designated above, and Met. is an alkali metal, ammonium or other basic radical with carbonyl dihalogenide represented by the formula COX_2 (wherein X is a chlorine atom or a bromine atom). The reaction may be carried out in a suitable solvent, for example, water, lower alkanols, chloroform, tetrahydrofuran, dioxane, acetone, or a mixture thereof as well as carbonyl dihalogenide itself, but water is most preferable. Generally speaking, carrying out the reaction in dilute solution may afford better results.

The starting compounds, thiol-type compounds, of Formula II, may be prepared by reacting the mineral acid salts of thiazolium-type thiamine or hydroxyethyl thiamine (HET) with alkaline substances, for example an alkali metal, an alkali metal hydroxide, an alkali metal alkoxide, an alkali metal carbonate and ammonium hydroxide according to a conventional manner.

The reagent, carbonyl dihalogenide (preferably phosgene) may be used in gaseous or liquid state, or as a solution of inert solvent, for example, benzene or chloroform, about equimolar amount or more to the starting material II in aqueous solvent and nearly equimolar amount in non aqueous solvent, for example, alcohol, acetone, chloroform, dioxane, and tetrahydrofuran.

Although the optimum reaction temperature should be based on the employed reagent and solvent, a temperature from −10°C to 10°C is normally adopted in order to prevent evaporation of the carbonyl dihalogenide and the side reaction.

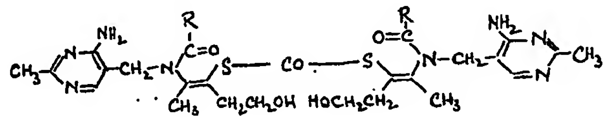
The reaction time is usually up to 2 hours preferably up to 1 hour. Occasionally

rapid reaction takes place as soon as the starting material and the reagent are mixed according to the properties of the reagent and solvent selected.

The addition of an acid combinable agent, for example alkali metal hydroxide, alkali metal carbonate, ammonium hydroxide and triethylamine to the reaction mixture during the reaction process afford better results because the pH of the reaction mixture tends to get acidic when an aqueous solvent is employed, and thiol-type thiamine derivatives II tend to get thiazolium-type in acidic conditions.

When lower alcohols are employed as a solvent, the reaction should be carried out at a temperature lower than −20°C to prevent the interaction of carbonyl dihalogenide and the lower alcohols.

When the reaction is carried out at a temperature lower than −10°C, di-thiamine-carbonates represented by formula III:



(III)

wherein R has the same significance as designated above, happen to be produced in the reaction mixture. This compound III is unstable in neutral or basic conditions whereby it turns promptly to the above-mentioned thiol-type thiamine derivatives of Formula I and thiamine or hydroxyethyl thiamine (HET). However, in acidic conditions, this compound III is stable and can be isolated according to a per se conventional manner. From thus obtained di-thiamine-carbonates of Formula III carbothiamine or carbohydroxyethylthiamine shown by formula I can be obtained by adding basic substances, for example, alkali metal hydroxide, alkali metal carbonate and ammonium hydroxide, and adjusting the solution from neutral to basic.

The recovery of thus prepared carbothiamine or carbohydroxyethylthiamine shown by Formula I from the reaction solution can be readily accomplished according to a conventional manner. For instance, the product is extracted with an organic solvent or the reaction mixture is concentrated after washing it.

Thus obtained thiol-type thiamine derivatives I may be refined by means of recrystallization from water, lower alcohols and ethylene dichloride, or by means of treatment with mineral acids, for example hydrochloric acid, in the course of the recovery process whereby the mineral acid salts suitable for purification and crystallization are obtained.

Above described Formula I, II and III each means the derivative of thiamine when R is a hydrogen atom, and the derivative of hydroxyethyl thiamine (HET) when R is an α-hydroxyethyl radical, in which an optically active product is obtained if an optically active starting compound is used. No racemization is seen to occur in the reaction processes. The thiol-type cyclic thiamine derivatives of Formula I and non-toxic organic and inorganic salts thereof have Vitamin B_1 activity. They are rapidly absorbed from the intestinal canal and maintained a high Vitamin B_1 level (about twice as high as TPD) in blood for a long time after oral administration.

Animal and clinical test data of compounds according to the present invention are shown in Tables I to VII in contrast with thiamine chloride hydrochloride and a commercially available typical active Vitamin B_1 agent, thiamine propyl disulfide (TPD) and S.O-dibenzoylthiamine.

In these tables, the compounds designated by an asterisk (*) are products of the present invention.

TABLE I

Changes of Vitamin B_1 Level in Blood After Oral Administration (Animal Test)

Time (hours)	Vitamin B_1 concentration in blood (μg/dl)						
	0	0.5	1	3	5	8	24
Thiamine chloride hydro chloride	29.8	31.5	35.1	42.0	40.2	39.3	34.8
Thiamine propyl disulfide	27.6	61.8	65.2	55.1	50.8	40.7	29.1
Carbo thiamine* ((I): R = H)	25.5	70.6	78.9	75.4	61.0	54.6	32.3

Test dosage: Amount equivalent to 5mg of thiamine chloride hydrochloride per kilogram of body weight.
Mode of administration: Oral
Test animals: Rabbits

TABLE II

Changes of Vitamin B_1 Level in Blood After Oral Administration (Animal Test)

Time (hours)	Vitamin B_1 concentration in blood (μg/dl)						
	0	0.5	1	3	5	8	24
Thiamine chloride hydrochloride	21.5	27.3	28.0	38.5	41.2	35.2	20.0
Dibenzoyl thiamine	25.4	51.9	59.9	70.5	61.3	52.8	27.6
Thiamine propyl disulfide	24.9	93.6	107.0	84.4	73.9	62.9	24.8
Carbothiamine* ((I): R = H)	23.6	145.0	158.2	160.1	142.5	116.	34.3

Test dosage: Amount equivalent to 10 mg of thiamine chloride hydrochloride per kilogram of body weight.

Mode of administration: Oral

Test animals: Rabbits

TABLE III

Changes of Vitamin B_1 Level in Blood After Oral Administration (Animal Test)

	Vitamin B_1 concentration in blood (μg/dl)						
Time (hours)	0	0.5	1	3	5	8	24
Thiamine chloride hydrochloride	25.7	33.3	36.6	39.4	43.4	39.7	35.9
Thiamine propyl disulfide	27.1	163.0	200.0	190.0	132.0	102.0	44.3
Carbothiamine* ((I) : R = H)	26.2	291.0	343.0	243.0	211.0	191.0	52.5

Test dosage: Amount equivalent to 20 mg of thiamine chloride hydrochloride per kilogram of body weight.

Mode of administration: Oral

Test Animals: Rabbits

TABLE IV

The Amount of Vitamin B_1 Excreted in Urine After Oral Administration

Test dosage equivalent to thiamine chloride hydrochloride	Vitamin B_1 amount in urine (mg)*		
	10mg	25 mg	50mg
Thiamine chloride hydrochloride	0.4	0.6	1.2
Thiamine propyl disulfide	1.6	3.2	8.6
Carbothiamine* ((I) : R = H)	2.0	4.9	11.3

* Measured 6 hrs. after administration

Mode of administration: Oral

Test subjects: Adult human (↑ o)

TABLE V

Changes of Vitamin B_1 Level in Blood After Intravenous Injection (Animal Test)

Time (hours)	Vitamin B_1 concentration in blood (μg/dl) 0	0.5	1	3	6
Thiamine chloride hydrochloride	27.6	275.0	181.0	67.0	44.0
Thiamine propyl disulfide	26.8	1059.0	954.0	739.0	540.0
Carbothiamine* ((I) : R = H)	25.8	412.0	352.0	250.0	178.5

Test dosage: Amount equivalent to 5 mg of thiamine chloride hydrochloride per kilogram of body weight.

Mode of administration: Intravenous

Test animals: Rabbits

TABLE VI

The Amount of Vitamin B_1 Excreted in Urine After Intravenous Injection (Animal Test)

Time (hours)	Vitamin B_1 amount in urine (mg) 0 — 1	1 — 3	3 — 6	6 — 24
Thiamine chloride hydrochloride	7.1	1.0	0.5	0.9
Thiamine propyl disulfide	3.4	1.3	1.0	2.6
Carbothiamine* ((I) : R = H)	4.5	0.9	0.6	1.5

Test dosage: Amount equivalent to 5 mg of thiamine chloride hydrochloride per kilogram of body weight.

Mode of administration. Intravenous (in ear)

Test animals: Rabbits

TABLE VII

Acute Toxicity (Animal Test)

Administration	LD_{50} (mg/kg) Intravenous	Oral
Thiamine chloride hydrochloride	119	9,000
Thiamine propyl disulfide	320	2,750
Carbothiamine* ((I) : R = H)	513	13,390

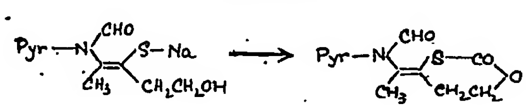
Test Animals: Mice

Carbothiamine or carbohydroxyethylthiamine (I) and the innoxious salts thereof have no such unpleasant smell as have thiamin propyl disulfide and the homologs thereof.

As shown in the above tables, the thiol-type thiamine derivative (I) is useful as an active Vitamin B_1 agent since the products of this invention are easily absorbed and have less toxic property. The products are used usefully for giving by oral administration a high Vitamin B_1 level in blood as achieved by injection.

Several suitable examples for effecting the process of this invention are shown below, in which the symbol "Pyr" means a (2-methyl-4-amino-5-pyrimidyl) methyl group.

EXAMPLE 1



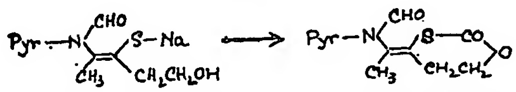
An aqueous solution of the sodium salt of thiol-type thiamine that has been prepared by adding 10g of thiamine chloride hydrochloride to 36.8ml of an aqueous 10% sodium hydroxide solution and allowing to stand for 30 minutes at room temperature was mixed with 3g of sodium bicarbonate and, after cooling to 0—3°C, to the mixture was added 2ml of phosgene during 30 minutes with stirring. After stirring for another 30 minutes at the same temperature, the temperature of the solution was raised to room temperature to remove excess phosgene. The product was extracted four times from the reaction mixture using 100ml portions of ethyl acetate. After drying the extract with anhydrous magnesium sulfate, the solvent was distilled off from the product under reduced pressure to give crystals. By rinsing with water and drying the crystals, 2.5g of the white crystals of the crude carbothiamine was obtained. When the crude carbothiamine was recrystallized from water, it had a decomposition point of 175.5°C.

The infrared spectrum of the carbothiamine showed the absorption of C=O at $1685cm^{-1}$ and the absorption of —CHO at $1660cm^{-1}$. The thiochrome reaction of the carbothiamine was negative but by treating it with cysteine the reaction was changed into positive.

Analysis — Calcd. for $C_{13}H_{10}N_4O_3S$: C, 50.61; H, 5.22; N, 18.17; S, 10.40. Found: C, 50.52; H, 5.36; N, 18.01; S, 10.35.

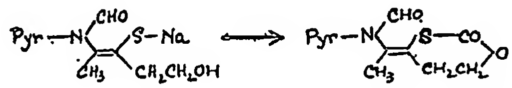
To the remaining aqueous layer after extracting with ethyl aceate was added an excess of a saturated aqueous ammonium thiocyanate solution and the solution was allowed to stand for 1 hour. The white crystals thus precipitated were filtered, rinsed with water, and dried to give 3g of thiamine thiocyanate having the melting point of 192°C.

EXAMPLE 2



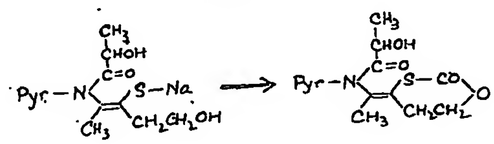
To an aqueous solution of the sodium salt of thiol-type thiamine that has been prepared as in Example 1 using 3.0g of thiamine chloride hydrochloride was added gradually 3ml of liquid phosgene while maintaining the reaction mixture in an alkaline state by adding occasionally an aqueous sodium hydroxide solution instead of adding acid sodium carbonate as in Example 1. After the reaction was finished, the product was extracted from the reaction mixture with ethyl acetate followed by subsequent treatment as in Example 1 to give 1.8g of white crystals of the carbothiamine showing the decomposition point of 173—174°C.

EXAMPLE 3



The reaction was conducted as in Example 2 by adding however 3.3ml of bromophosgene instead of phosgene to a solution of the sodium salt of thiol-type thiamine that has been prepared as in Example 1 using 3.0g of thiamine chloride hydrochloride. By treating the thus obtained reaction mixture as in Example 1, 1.5g of white crystals of the carbothiamine showing the decomposition point of 174—175°C was obtained.

EXAMPLE 4

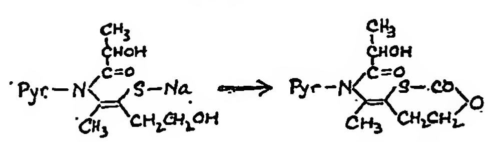


In a mixture of 100ml of water and 39.4ml of an aqueous 1 N sodium hydroxide solution was dissolved 5g of hydroxyethyl thiamine (HET) chloride hydrochloride and the mixture was allowed to stand for 1 hour at room temperature. To the solution was added dropwise 1.5ml of phosgene during 30 minutes with stirring under cooling to 3—5°C. During this procedure, the reaction solution was maintained alkaline by adding an aqueous 1 N sodium hydroxide solution to it.

From the reaction solution the product was extracted with four 100ml portions of ethyl acetate. After drying the extract with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure and by rinsing the thus obtained crystals with a small quantity of ethyl acetate, 2.5g of white crystals of the crude carbohydroxyethyl thiamine was obtained. The crude product was recrystallized from ethanolic water to give a product having a decomposition point of 195—197°C. The infrared spectrum of the carbohydroxyethyl thiamine showed the absorption band of C=O at 1705cm^{-1} and the absorption band of —N—CO at 1650cm^{-1}. The thiochrome reaction of the carbohydroxyethyl thiamine was negative but upon treating it with cysteine, the reaction was changed into positive.

Analysis — Calcd. for $C_{15}H_{20}N_4O_4S$: C, 51.12; H, 5.72; N, 15.90; Found: C, 51.15; H, 5.78; N, 15.99.

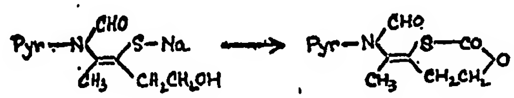
EXAMPLE 5



$[\alpha]_D^{23} -28.7$

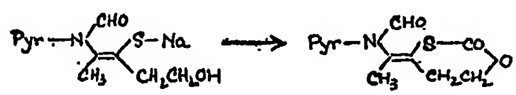
By treating 5.0g of d-hydroxyethyl thiamine (d-HET) chloride hydrochloride ($[\alpha]_D^{23}$ + 11.7 (C = 2.0, in H_2O)) as in Example 4, 2.6g of the optically active carbohydroxyethyl thiamine with a decomposition point of 195—196°C was obtained. The product showed the specific rotation $[\alpha]_D^{23}$ − 28.7 (c = 1.2, in 0.1 N HCl).

EXAMPLE 6



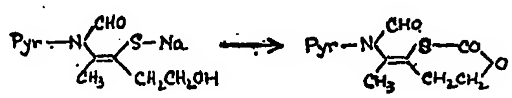
In 30ml of absolute ethanol was dissolved 3g of the sodium salt of thiol-type thiamine. Then, under cooling to $-20°C$, 1g of phosgene in 5ml of benzene was gradually added dropwise to the solution, and after stirring for 10 minutes at the same temperature, the mixture was further stirred for another 10 minutes at room temperature. The NaCl deposited during the reaction was removed by filtration from the reaction solution and, after concentrating the filtrate, the residue was dissolved in water and the solution was neutralized by sodium bicarbonate. The product thus extracted from the solution with ethyl acetate and the extract was, afer drying with anhydrous sodium sulfate, concentrated, whereby the residue was crystallized. The crystals were recovered by filtration and rinsed with a small amount of ethanol and then ethyl acetate to give 0.3g of the crude carbothiamine with a decomposition point of 174—175°C. When the crude crystals were recrystallized from ethylene dichloride, they had a decomposition point of 182°C. Further, by treating the carbothiamine with nitric acid, the nitrate (recrystallized from methanol-ethylacetate) with a decomposition point of 137—138°C was obtained.

EXAMPLE 7



Three grams (3g) of the sodium salt of thiol-type thiamine was dissolved in 30ml of absolute methanol and to the solution was gradually added dropwise under cooling to $-20°C$ a solution of 1.9g of bromophosgene in 10ml of benzene. By treating the thus prepared solution as in Example 6, 0.3g of the carbothiamine with a decomposition point of 175°C was obtained.

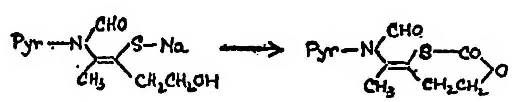
EXAMPLE 8



In 50ml of chloroform was suspended 3.0g of the dried sodium salt of thiol-type thiamine. Under cooling with ice and stirring, a solution of 0.7g of phosgene in 10ml of benzene was added to the suspension dropwise. Then, after continuing stirring for 1 hour at the same temperature, the solution was mixed with 1 ml of triethylamine with thorough stirring and then further was mixed with 20ml of water with thorough stirring.

After separating the chloroform layer from the reaction solution and drying the layer with anhydrous magnesium sulfate, the product was concentrated and the residue was crystallized with addition of a small amount of ethyl acetate. The crystals were recovered by filtration and rinsed with ethyl acetate to give 0.9g of white crystals of the product having a decomposition point of 173°C.

EXAMPLE 9

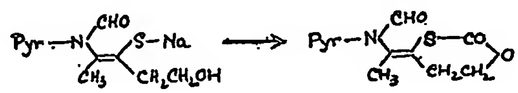


In 50ml of dioxane was suspended 3g of the sodium salt of thiol-type thiamine and to the suspension was added dropwise a solution of 1g of phosgene in 5ml of benzene under ice-cooling. The mixture was then stirred for 1 hour at the same

temperature. After reaction, the solvent was distilled off under reduced pressure, and the residue was dissolved in water, and the solution was neutralized with the addition of sodium bicarbonate. From the solution was extracted the product with ethyl acetate and, after drying the extract, the product was treated with dried hydrogen chloride gas to deposite white crystals. The crystals were recovered by filtration and recrystallized from methanolethyl acetate to give 1.0g of the hydrochloride of the carbothiamine having a decomposition point of 178—179°C.

Analysis — Calcd. for $C_{13}H_{10}N_4O_3S.HCl$: Cl, 10.30. Found: Cl, 10.22.

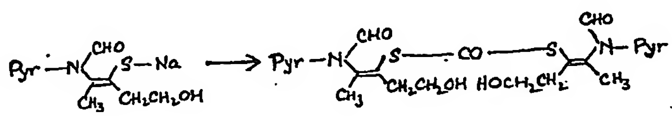
Example 10



In 60ml of tetrahydrofuran was suspended 3g of the sodium salt of thiol-type thiamine and under cooling with ice water, a solution of 1.9g of bromophosgene in 10ml of benzene was added gradually to the suspension dropwise. The white crystals obtained by treating the mixture as in Example 9 were recrystallized from ethylene dichloride to give 0.9g of the hydrochloride of the carbothiamine with a decomposition point of 179—180°C.

Example 11

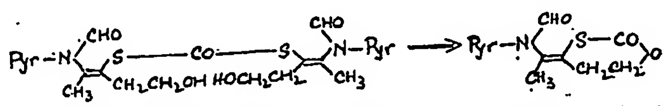
(A)



In 48ml of a 10% aqueous sodium hydroxide solution was dissolved 13.5g of thiamine chloride hydrochloride and the solution was allowed to stand for 30 minutes at room temperature. To the solution was added 50ml of ethanol and under cooling to −20°C was added dropwise a solution of 3ml of phosgene in 30ml of benzene with stirring followed by stirring for 10 minutes at the same temperature. The reaction mixture was then mixed with diluted hydrochloric acid at the same temperature to adjust the pH to 2 and concentrated under reduced pressure to a half. The solution obtained was neutralized with the addition of sodium bicarbonate and the product was extracted five times with chloroform. After drying quickly with anhydrous magnesium sulfate, the extract was mixed with ethanolic hydrochloric acid to be converted into an acid state and then dried by evaporating under reduced pressure. By adding acetone to the residue, the white powder of dithiamine-carbonate dihydrochloride was obtained. By recrystallizing the crude product from isobutanol, 8.4g of needles with a decomposition point of 129—130°C was obtained.

Analysis — Calcd. for $C_{25}H_{36}N_8O_5S_2Cl_4.H_2O$: C, 44.05; H, 5.61; N, 16.43. Found: C, 44.12; H, 6.15; N, 16.18.

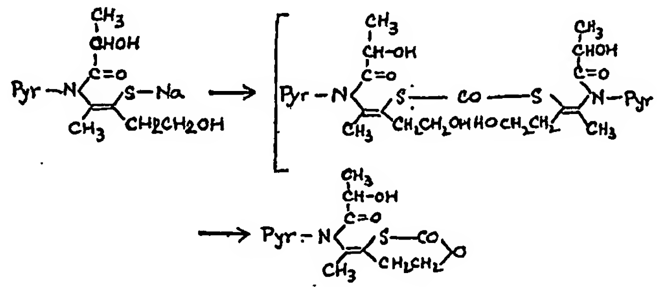
(B)



In 10ml of water was dissolved 2.0g of the dithiamine-carbonate dihydrochloride that had been obtained in process (A) and after adding 6ml of an aqueous 1 N sodium hydroxide solution, the solution was allowed to stand for 15 minutes at 45°C. After cooling, the product was extracted from the reaction mixture with ethylene dichloride and the extract was dried with anhydrous magnesium sulfate followed by concentration to give 0.6g of product with a decomposition point of 177—179°C.

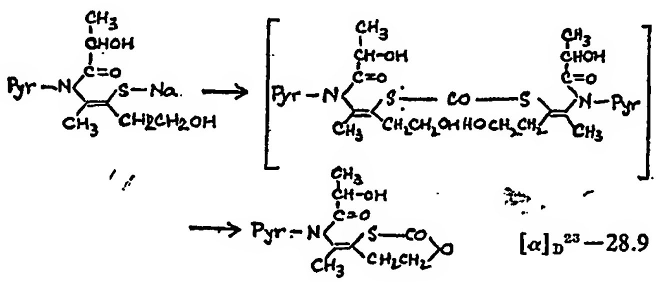
The residual aqueous layer after extracting with ethylene dichloride was mixed with diluted hydrochloric acid to convert the pH to 6.5 and then mixed with 1g of ammonium thiocyanate to precipitate crystals. By recovering the crystals with filtration and water-rinsing and drying them, 0.9g of thiamine thiocyanate was obtained.

EXAMPLE 12



In 16ml of an aqueous 10% sodium hydroxide solution was dissolved 5.0g of hydroxyethyl thiamine (HET) chloride hydrochloride and the solution was allowed to stand for 30 minutes at room temperature. After adding 16ml of ethanol to the solution, the solution was cooled to −20°C. To the solution was added under stirring dropwise a solution of 1.5g of phosgene in 15ml of benzene and the solution was stirred for 10 minutes at the same temperature. The pH of the solution was adjusted to 2 at the same temperature with addition of diluted hydrochloric acid and the solution was concentrated to about a half under reduced pressure. It was confirmed by a paper chromatography (developed in: n-butanol : acetic acid : water=4 : 1 : 5) that besides a small amount of hydroxyethyl thiamine (HET), di-(hydroxyethyl thiamine)-carbonate was mainly present in thus obtained solution. The pH of the solution was adjusted to 9 by adding sodium carbonate and, after allowing to stand for 10 minutes, the product was extracted with ethylene dichloride. The extract was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give 1.4g of the carbohydroxyethyl thiamine with a decomposition point of 194—196°C.

EXAMPLE 13

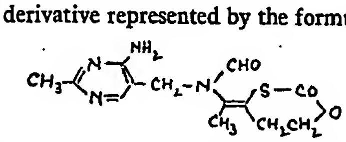


$[\alpha]_D^{23}$ −28.9

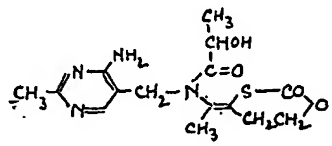
By repeating the procedure as in Example 12 using 5g of d-hydroxyethyl thiamine (d-HET) chloride hydrochloride ($[\alpha]_D^{23}$ + 11.7 (c=2.0, in H_2O)), 1.5g of the optically active carbohydroxyethyl thiamine with a decomposition point of 194°C was obtained. The product showed the specific rotation $[\alpha]_D^{23}$ − 28.9 (c=1.2, in 0.1 N HCl).

WHAT WE CLAIM IS:—

1. A thiol-type thiamine derivative represented by the formula



2. A thiol-type thiamine derivative represented by the formula



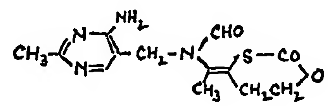
3. An optically active d-form of the thiol-type thiamine derivative claimed in claim 2.

4. The optically active l-form of the thiol-type thiamine derivative claimed in claim 2.

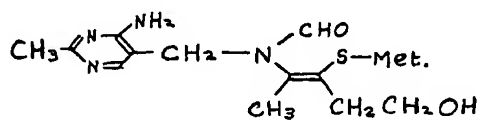
5. A therapeutically useful acid salt of a thiol-type thiamine derivative as claimed in any of claims 1 to 4.

6. A thiol-type thiamine derivative according to claim 1 substantially as hereinbefore described with reference to any of the Examples 1, 2, 3 and 6 to 11.

7. A process for preparing a thiol-type thiamine derivative represented by the formula



which comprises reacting a thiol-type thiamine derivative represented by the formula



where Met. is an alkali metal, ammonium or other basic radical and a carbonyl dihalogenide represented by the formula COX_2 (wherein X is a chlorine atom or a bromine atom) in a basic state.

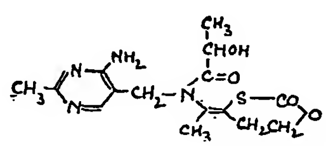
8. A process as claimed in Claim 7 wherein the carbonyl dihalogenide is phosgene.

9. A process as claimed in Claim 7 wherein the carbonyl dihalogenide is bromophosgene.

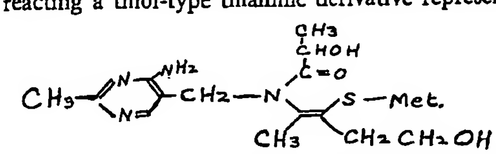
10. A process as claimed in Claim 7 wherein the reaction is carried out in an alcohol at a temperature below $-20°C$.

11. A process as claimed in Claim 7 wherein the reaction is carried out in a non-aqueous solvent.

12. A process for preparing a thiol-type thiamine derivative represented by the formula



which formula refers to the dl-form and the optically active d-form and l-form, which process comprises reacting a thiol-type thiamine derivative represented by the formula

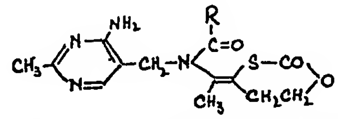


wherein Met. is an alkali metal, ammonium or other basic radical and a carbonyl dihalogenide represented by the formula COX_2 (wherein X is a chlorine atom or a bromine atom) in a basic state.

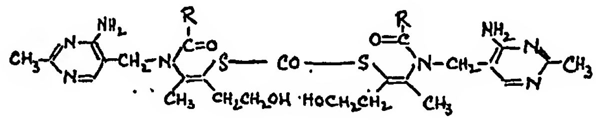
13. A process as claimed in Claim 12 wherein the carbonyl dihalogenide is phosgene.

14. A process as claimed in Claim 12 wherein the carbonyl dihalogenide is bromophosgene.

15. A process for preparing a thiol-type thiamine derivative represented by the formula



wherein R is a hydrogen atom or an α-hydroxyethyl group, and where R is an α-hydroxyethyl group, the formula refers to the dl-form and the optically active d-form and l-form, which process comprises adding a basic substance consisting of an alkali metal hydroxide, an alkali metal carbonate or ammonium hydroxide to a dithiamine-carbonate derivative represented by the formula



wherein R has the same significance as defined above whereby the reaction mixture is converted from a neutral to an alkaline state.

16. A process for preparing a thiol-type thiamine derivative according to Claim 1 substantially as described in Example 1 herein.

17. A process for preparing a thiol-type thiamine derivative according to Claim 1 substantially as described in Example 3 herein.

18. A process for preparing a thiol-type thiamine derivative according to Claim 2 substantially as described in Example 4 herein.

19. A process for preparing a thiol-type thiamine derivative according to Claim 1 substantially as described in Example 6 and 7 herein.

20. A process for preparing a thiol-type thiamine derivative according to Claim 1 substantially as described in any of Examples 8, 9 or 10 herein.

21. A process for preparing a thiol-type thiamine derivative according to Claim 2 substantially as described in Example 12 herein.

22. A process for preparing a thiol-type thiamine derivative according to Claim 1 substantially as described in any of Examples 2 and 11 herein.

23. A process for preparing a thiol-type thiamine derivative according to claim 2 substantially as described in Example 5 or 13 herein.

24. A process as claimed in claim 7 wherein the reaction is carried out in water.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.